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Research Article

Treatment Response to Sertraline in the Pakistani population and its association with Cytochrome P450 2C19 Genotypes

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Abstract

Selective serotonin reuptake inhibitors (SSRIs) are metabolized differently depending on variations in the *CYP2C19* gene. Clinical practitioners are using pharmacogenetic information based on the impact of *CYP2C19* polymorphisms more frequently. Yet, the fundamental tenets connecting distinct metabolism to efficacy or adverse drug reactions are still poorly understood. The objective of this study was to determine the *CYP2C19**2, *3, and *17 allele and genotype frequencies among the treatment-responsive and resistant patients and their correlation with the response and to determine the association of *CYP2C19* allele to adverse effects of sertraline in major depressive disorder (MDD) patients. The study was conducted at the Institute of Pharmaceutical Sciences, Khyber Medical University. Fifty patients of MDD were recruited from a psychiatric clinic to take part in this study. Three scales, Hamilton Depression Rating Scale (HDRS or HAMD-17), General Medication Adherence Scale (*GMAS),* and Liverpool University Neuroleptic Side Effect Rating Scale (*LUNSERS*) were used to assess depression severity, adherence to drug therapy, and adverse effects respectively at baseline and then at weeks 2, 4, 6 and finally at 6 months. 3ml blood was also taken from patients for genotyping polymorphic variants of *CYP2C19*. We found that the risk factors for depression as indicated by our study are females (58%) OR 1.18 as compared to males OR 0.75, married individuals (74%), and poor socioeconomic status (40%). A high response rate to sertraline was recorded with 82% responders and only 18% non-responders. Response rate of males was slightly higher than females at 92% and 90% respectively. HAMD 1st follow-up was significantly correlated to baseline score at p-value 0.01. GMAS was negatively correlated to HAMD with an R-value of -0.042. We found no significant association between *CYP2C19* genotypes and sertraline therapeutic response or adverse effects. However, the study showed that adherence to drug therapy leads to better treatment response.

Keywords: CYP2C19, Sertraline, Major Depressive Disorder, Depression, Single Nucleotide Polymorphism, Genetic Variation

1. Introduction

Depression or major depressive disorder (MDD) is one of the most common ailments affecting the world population, with a global prevalence of 3.8% (Organization 2023). Although an array of treatment options are available, selective serotonin reuptake inhibitors (SSRIs) are considered the mainstay (Montano et al. 2023). However, one of the main caveats to the use of SSRI is its interindividual variation in drug response (Li et al. 2020). Sertraline is one of the most commonly used SSRIs in psychiatry. Differential response to Sertraline has mainly been attributed to variation in its pharmacokinetics (PK).

About one-tenth of all therapeutically indicated medications, such as antidepressants, anticonvulsants, proton pump inhibitors, antipsychotics, and antiplatelets, are metabolized by the crucial CYP2C19 enzyme from the CYP450 family (Scott et al. 2013). Variability in responsiveness or an increase in undesirable outcomes are believed to result from interindividual genetic differences of these enzyme systems. Ultrarapid metabolizers

(UM) for increased enzymatic function, extensive metabolizers (EM-also known as normal metabolizers), intermediate metabolizers (IM) for decreased enzymatic function, and poor metabolizers (PM) for no enzymatic function can be classified based on the level of enzymatic activity (Aldrich et al. 2019). The *CYP2C19* gene, which has nine exons and eight introns and is found on the region of chromosome 10 known as 10q24.1 to 10q24.3, codes for a protein of 490 amino acid residues. The exonic region of the *CYP2C19* gene has about 25 genetic variants, of which the common variants are linked to changes in drug metabolism; the presence of the polymorphisms 681GA, 636 GA, and 806 CT, resulting in the *CYP2C19**2, *CYP2C19**3, and *CYP2C19**17 alleles respectively, (Dehbozorgi et al. 2018). Variant *CYP2C19**2 results from the change from guanine (G) to adenine (A) at position 6681 in exon 5 (rs4244285), producing frequent problems in all populations (Buzoianu et al. 2010). The most prevalent alleles, *CYP2C19**2 and *CYP2C19**3, encode enzymes with reduced activity (Beitelshees et al. 2011). In case of *CYP2C19**3, a point mutation in exon 4 causes a premature stop codon, rendering the protein inactive (Hamdy et al. 2002). A -806 CT SNP called *CYP2C19**17 (rs 12248560) may result in precise nuclear protein binding to the 5' flanking region. Hence, this binding results in elevated enzymatic activity and increased gene transcription (Sim et al. 2006).

Sertraline pharmacokinetics appear to be most affected by *CYP2C19* variations. Individuals with *CYP2C19* (PMs), or those with the *2 or *3 no-function alleles, have a much lower rate of desmethylsertraline synthesis than *CYP2C19* normal metabolizers (NMs), which results in higher exposure to the pharmacologically active parent molecule (Grasmäder et al. 2004a). A 50% dose decrease may be required for PM of sertraline, according to extrapolations of the drug's dose based on pharmacokinetic properties among *CYP2C19* phenotypes (Stingl, Brockmöller, and Viviani 2013). A recent investigation on a retrospective cohort of children and adolescents with anxiety and depressive disorders discovered that the frequency of *CYP2C19* no-function alleles affected the rate of sertraline titration (Ethan A. Poweleit 2019). The enhanced function *CYP2C19**17 allele has not been found to significantly alter sertraline plasma concentrations (Rudberg et al. 2008). There are established clinical guidelines for sertraline use in *CYP2C19* PMs. These include the Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, which advises clinicians treating *CYP2C19* PMs to think about lowering the starting dose by 50% before titrating to response or choosing an alternative antidepressant not primarily metabolized by *CYP2C19* due to the risk of increased side effects (Hicks et al. 2015). Moreover, utilizing lower doses in patients who are *CYP2C19* PMs is advised by the Pharmacogenetics Working Group (DPWG) of the Royal Netherlands Pharmacists Association (Swen et al. 2011). Although a significant body of evidence suggests a role of genetics in treatment response to SSRIs, there is no study showing if (and how much) genetic variation/s in the *CYP2C19* gene would have any effects on the clinical outcome of sertraline therapy in the population of Northern Pakistan. The present investigation was undertaken to address this knowledge gap.

2. Methods & Materials

The study was conducted at Khyber Medical University (KMU), Institute of Pharmaceutical Sciences (IPS), Peshawar, Pakistan. Clinically diagnosed, both treatment-naïve patients and those who have been on sertraline for not more than six months, were enrolled at Dr. Shafiq Psychiatric Hospital, University Road, Peshawar. Informed consents were obtained from all the patients. For determining the

Table 1: Treatment phase and response of MDD patients with Sertraline therapy.

Treatment Phase		Response	
Naïve n (%)	**On Treatment** n (%)	**Yes** n (%)	**No** n (%)
7 (14)	43 (36)	41(82)	9(18)

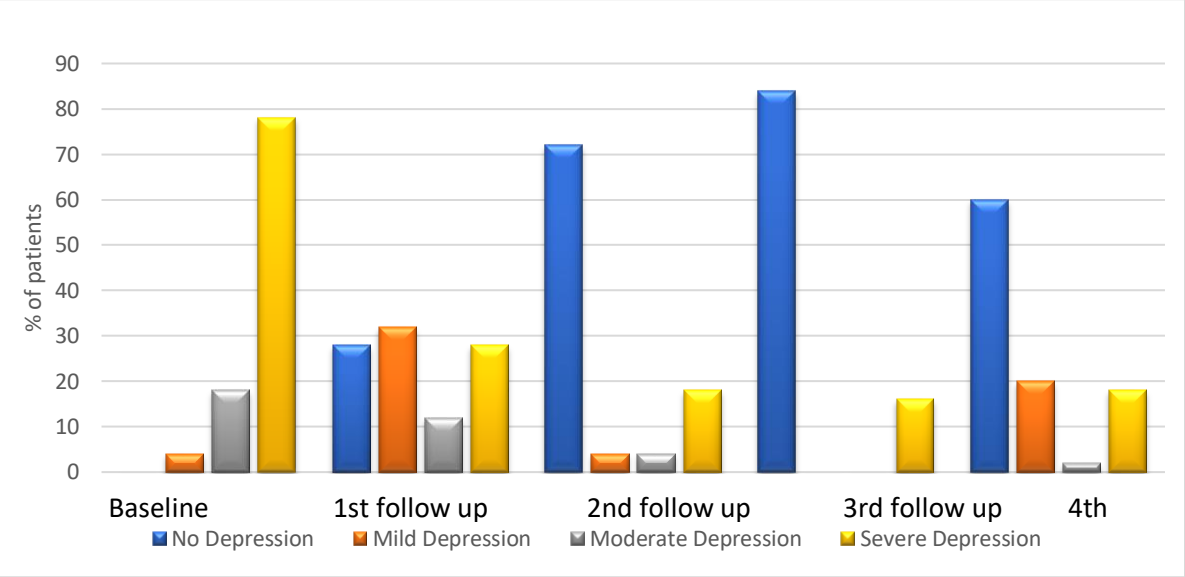

Figure 1: Effect of Sertraline on HAMD Score at baseline and follow-ups

This figure shows the therapeutic response to sertraline in the studied cohort at baseline (day 1 of treatment), at 1st follow-up (2 weeks), at 2nd follow-up (4 weeks), at 3rd follow-up (6 weeks), and at 4th follow-up (6 months). The graph shows a positive therapeutic trend at all follow-ups, but more so at 1st follow-up point.

efficacy of sertraline, all participants in the study were assessed using the Hamilton Depression Rating Scale (HDRS or HAMD) scale. The patients were interviewed at day 1 of enrollment to establish a baseline HAMD score. Further interviews for evaluation of change in depression severity were consequently conducted on weeks 2, 4, 6, and at 6 months.

Patients who reported a 50% reduction in HDRS or HAMD score from baseline at the last interview i.e. at 6 months, were considered responsive while others were considered non-responsive (Henkel, Seemüller, Obermeier, Adli, Bauer, Mundt, Brieger, Laux, Bender, Heuser, et al. 2009). All patients were evaluated for adherence to sertraline therapy on weeks 2, 4, and 6 and later at 6 months using the General Medication Adherence Scale (GMAS) (Naqvi et al. 2018). To evaluate the adverse drug reactions (ADR) of sertraline therapy in-person and telephonic interviews were conducted using the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) questionnaire at 6-months (Morrison et al. 2000).

For genetic analysis, a peripheral blood sample (approximately 3 ml) was collected in 5ml syringe from each participant, and DNA was extracted using a modified salting-out method (Chacon-Cortes and Griffiths 2014). Genotyping of the DNA sample was done using the direct Sanger sequencing method. Flanking regions of rs4244285, rs4986893, and rs12248560 were amplified through polymerase chain reaction (PCR). A 20 ul reaction was set up for each SNP, which consisted of 4 ul of PCR master mix (5x), 0.4 ul each of reverse and forward primers (10 uM), and 1 ul of template DNA (50 ng/ul). Out of this reaction mix, 5 ul of PCR product

Table 2: This table shows therapy compliance using the GMAS scale.

GMAS categories	Adherence %age
Low Adherence	2%
Partial Adherence	14%
Good Adherence	38%
High Adherence	46%

Table 3. Association of Sertraline response to demographics.

Variable	Response	Number	Mean±Std deviation	Value of t	P value	95% CI
Age	No response	9	34.5±11.3	-0.001	0.999	-8.72/8.71
	Response	41	34.5±11.8	-0.001	0.999	9.20/9.19
Gender	No response	9	0.33±0.50	-0.572	0.570	-0.47/0.26
	Response	41	0.43±0.50	-0.574	0.577	-0.50/0.29
Marital Status	No response	9	0.66±0.50	-0.805	0.425	-0.48/0.206
	Response	41	0.80±0.45	-0.762	0.462	-0.53/0.26
Socioeconomic status	No response	9	1.44±1.23	1.72	0.090	-0.096/1.277
	Response	41	0.85±0.85	1.36	0.203	-0.37/1.55

was loaded onto agarose gel (1.2%), along with size marker (100 bp ladder) for confirmation. The remaining PCR product was cleaned up through ethanol and used as a template for cycle sequencing using Big Dye Terminator™. The sequencing reaction was recovered using ethanolic extraction and loaded onto Seqstudio ™ (Life Technologies). Output sequence files were analyzed by NCBI Blast and FinchTV ™.

The data analysis was done using SPSS software for Windows. The independent variables were age, gender, BMI, socioeconomics, comorbidity, family history, and ethnicity while the dependent variables of the study were HAM-D 17 scoring (for drug efficacy), and LUNSERS scale (for adverse effects). Data distribution was checked for normality. Standard deviation and mean were presented for the numerical variables. Percentage and frequency were used for categorical variables. Pearson correlation was used to assess the strength of the association. Allele and genotype frequencies were counted manually. The $\chi 2$-test was used to assess the relationship between genotype and treatment response and for the determination of Hardy –Weinberg equilibrium.

3. Results

Of the total 50 patients, 7 (14%) were Sertraline naive while 43 (36%) were already on Sertraline treatment. Nine (18%) patients showed no response to the standard therapy after 6 months while 41(82%) patients showed positive response to therapy.

3.1. GMAS Scores

Adherence to Sertraline therapy was measured using the GMAS scale. Low adherence was seen in 1(2%) participant, partial adherence in 7(14%), good adherence in 19(38%), and high adherence in 23 (46%) as shown in Table 2

3.2. HAMD Baseline Score Association with Follow-up Scores

A paired sample t-test was used to determine the association of HAMD baseline score with 1st, 2nd, 3rd, and 4th follow-up. 1st follow-up was significantly associated with the HAMD baseline score with a p-value of 0.01. 2nd, 3rd, and 4th follow-ups did not display any significant association to baseline score as indicated by p-values of 0.13, 0.35, and 0.09 respectively (Table 5).

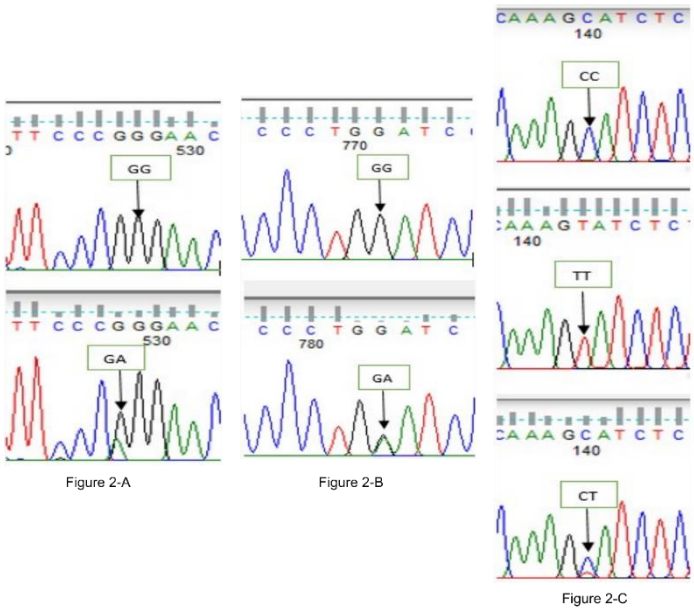

Figure 2. Sequencing Chromatograms of Patient Samples.
Figures 2A and 2B show major homozygous and heterozygous alleles of rs4244285 and rs4986893 as indicated by marked peaks, respectively. Whereas, 2C shows all three genotypes of rs12248560.

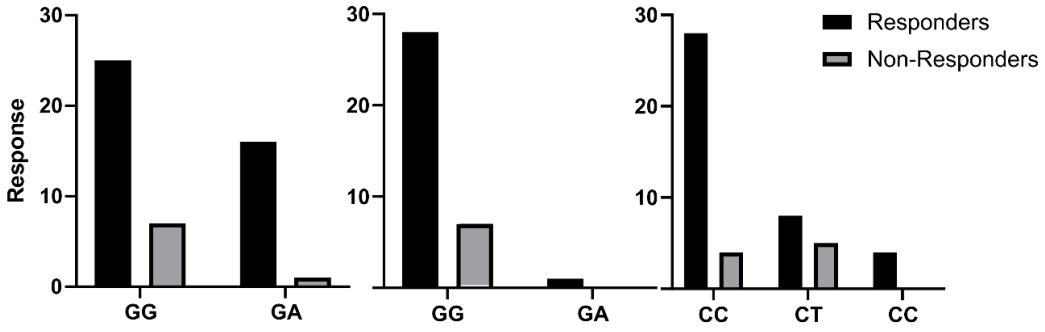

Figure 3: *CYP2C19* Genotype Frequencies.
Figures 3-A and 3-B show genotype distribution for major homozygous and heterozygous alleles of rs4244285 and rs4986893, respectively. A homozygous minor was not detected in either SNP. While 3-C shows all three genotypes of rs12248560 in Sertraline responders and non-responders.

3.3. Association Between *CYP2C19* Genotypes and Response

The frequency of various genotypes of the three investigated SNPs through sequencing is summarized in Table 4. For rs4244285, (49 sequences were detected), the GG genotype was found in 25 responders while 16 responders possessed the GA phenotype resulting in a p-value of 0.233 (table 4). Similarly, for rs4986893, (detected in only 36 samples) the GG genotype was found in 28 responders while 1 responder possessed the GA phenotype resulting in a p-value of 0.9. For rs12248560, (49 sequences were detected) the CC genotype was found in 28 responders and 8 responders

possessed the CT phenotype resulting in a p-value of 0.09 (table 4).. One sample displayed inconclusive results for all three SNPs due to poor quality of DNA. While in 14 samples rs498693 was not detected through sequencing.

3.4. LUNSERS Scores

The LUNSERS scale was administered after 6 months to study the adverse effects of sertraline. A very low range ADR is shown by 68% of patients, low ADR by 22%, average ADR by 6%, and high ADR by 4% of patients (table 5).

4. Discussion

Antidepressants, particularly SSRIs, have become a staple in a very high number of prescriptions. However, response to these drugs is quite variable, and predicting a clinical outcome would require considering all the important variables including (but not limited to) genetic diversity. This study aimed to elucidate the statistical association of *CYP2C19* genetic variants with treatment response to sertraline, which could contribute to personalized and effective therapeutic approaches in mental health management. The main outcome of our study of strikingly large proportion of patients responding to sertraline, which is rather discordant with the bulk of available literature. However, our data showed no significant association between drug response and *CYP2C19* variants.

This study was conducted in the Khyber Pakhtunkhwa area of Pakistan on a small sample size of 50 MDD patients. We recruited both male and female individuals between the ages of 18 and 65 years with a mean age of 34.56±11.6.

Table 4. Association between CYP2C19 genotypes and Sertraline response.

Variable	rs4244285		P-value
	Responder	Non-Responders	
GG	25	7	Ref
GA	16	1	0.233
	rs4986893		
	Responder	Non-Responders	
GG	28	7	Ref
GA	1	0	0.9
	rs12248560		
	Responders	Non-Responders	
CC	28	4	Ref
CT	8	5	0.09
TT	4	0	0.9

Table 5.: HAMD Baseline correlation with all follow-ups.

Variables	Mean ± Std. Deviation	*p*-value	95% confidence interval
HAMD baseline-1st follow-up	1.38±1.027	**0.01**	1.08/1.67
HAMD baseline- 2nd follow-up	2.08±1.192	0.135	1.74/2.41
HAMD baseline- 3rd follow-up	2.20±1.212	0.355	1.85/2.54
HAMD baseline- 4th follow-up	1.96±1.142	0.092	1.63/2.28

More females (58%) were found in our study compared to males (42%). This may be due to frequent hormonal changes especially changes in estrogen levels, emotional personality traits, and various family stressors. Societal pressures and taboos associated with mental health problems are also important factors. A higher depression rate was found in married individuals (74%) as compared to unmarried subjects (24%) which correlate with previous studies (Serretti et al. 2009). Socioeconomic status was divided into 3 categories according to monthly income/expenditure. 40% belonged to the poor, 30% to the fair, 24% to the good category, and 6% to the excellent category.

According to the HAMD score at baseline, 4% of participants had mild, 18% had moderate and 78% had severe depression. The minimum HAMD score at baseline was 13 and the maximum was 44 with a mean value of 24.86±8.18. The scores at 1st, 2nd, 3rd and 4th follow ups were recorded at 20.54±7.7, 14.42±7.9, 10.94±7.1, 8.98±7.7 and 7.82±7.86, respectively. Thus, at the end of 6 months of study, 60% of individuals were found to be in remission, 20% had mild; only 2% with moderate and 18% had severe depression. When HAMD follow-ups were correlated to baseline score only 1st follow-up (at 2 weeks) was significantly correlated with a p-value of 0.01 hence it can be said that two weeks is a good end point for therapy response, while 2nd, the 3rd and 4th follow ups were not significantly correlated with p-values at 0.135, 0.355 and 0.092 respectively.

Responders were recorded as participants showing a 50% reduction in HAMD score at 6 months from the baseline HAMD score (Henkel, Seemüller, Obermeier, Adli, Bauer, Mundt, Brieger, Laux, Bender, and Heuser 2009). Sertraline was found to be therapeutically efficacious as indicated by a large number of responders at 82%. In males, the response rate was 92% while in females it was 90%. Only 8% of males and 10% females were non-responders. The high response rate can be attributed to the fact that most of the study subjects were already on treatment with sertraline and some had switched to sertraline from other antidepressants. It can also be correlated to adherence to drug therapy measured by the GMAS scale. Low adherence was seen in only 2%, partial adherence in 14%, good adherence in 38%, and high adherence in 46% of patients. This shows a negative correlation of GMAS with HAMD as suggested by R-value -0.042. The greater the GMAS score (adherence), the lower the HAMD score indicating a better response. No significant association of HAMD score and LUNSERS score with response was found.

A six-month comparative study between Sertraline and paroxetine therapy showed sustained efficacy during continuation therapy. Sertraline had a lower relapse rate (2%) compared to paroxetine (9%). Continuation therapy significantly increased remission rates, with sertraline increasing from 52% to 80% and paroxetine from 57% to 74%. Quality of life improvements correlated with reduced depression scores. SSRIs also positively affected both categorical and dimensional measures of personality (Åberg-Wistedt et al. 2000). In the current study, adverse effects of sertraline therapy were studied by administering a LUNSERS questionnaire at 6 months. The commonest side effects seen were fatigue (64%), dry mouth (26%), tremors (12%), nausea (10%), syncope (6%), sexual dysfunction in males (4%), and headache (2%). Similar adverse effects were reported in Indian and Iranian Cohorts.

A study conducted by (Serretti et al. 2009) showed that in European patients' antidepressant responses were not significantly influenced by variability in CYP450 genes. Similar negative results regarding *CYP2C19* genetic variants to escitalopram response have also been observed (Peters et al. 2008). Multiple isoenzymes, including CYP2D6, CYP3A4, CYP2C9, and CYP2C19, are involved in the

metabolism of sertraline *in vivo*, according to research done in 2004 by (Grasmäder et al. 2004b). As a result, it is unlikely that changes in the metabolic capacity of a single isoenzyme significantly alter sertraline plasma concentrations and subsequently affect the therapeutic efficacy of sertraline. Therefore, despite the fact that the majority of antidepressants are CYP450 substrates, some additional factors must be involved in response variability (Vizirianakis 2014). To the best of our knowledge, genetic variations of *CYP450* genes do not always forecast responses to antidepressants. However, they may forecast adverse outcomes or plasma concentrations of SSRIs. Effects are strictly linked to drug plasma concentrations and functional variants of *CYP450* genes are linked with transformed enzyme activities (Zhang et al. 2014). We conclude that C*YP2C19* may modify the response to antidepressants, although they do not seem to be key players in antidepressant response.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

This study was approved by the ethical committee of Khyber Medical University (KMU/IPS/PG/IREB/1st meeting/2024/5), and informed consent for each patient was received, and dually signed by both the patient/guardian and researcher taking the consent.

Consent Forms

Consent forms are available with the authors.

Data Availability

All the data related to this study are available with the authors.

Authors Contribution

HZK and ZS conceptualized the study and performed the experiment and basic analysis. IK and MA helped with experiments performed the experiments, JA helped with the final analysis, preparation, and proofreading of the manuscript,

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